

Chapter XVI-3

HEMATOLOGICAL VARIABLES

In this section, 8 hematological variables are reported. These 8 variables are listed in Table XVI-3-1 along with abbreviations used, units of measure, and normal ranges employed in the analyses. Ranch Hand-comparison group differences have been analyzed using general linear models with all variables except the group indicator treated as continuous variables. Group differences have also been evaluated using log-linear models with all variables treated as categorical. In both the general linear and log-linear model analyses, the hematological variables were adjusted for smoking history available from the questionnaire as pack-years of cigarette use (Wintrobe, 1974). In the general linear models analyses, pack-years were used directly as a continuous variable. In the log-linear models, smoking history was treated as a tricotomous variable by grouping together: (1) nonsmokers, (2) smokers with 10 pack-years or less contact, and (3) smokers with greater than 10 pack-years cigarette smoking. Also, in the log-linear models analyses, the dependent (hematologic) variable was dichotomized as normal (within range) or abnormal (out of range). Analyses using the exposure index were also accomplished using the Ranch Hand participant data. These within-group analyses were performed in much the same manner as the Ranch Hand-comparison group contrasts, except that in the within-group analyses, exposure category took the place of the cohort indicator. Data on all Ranch Hand and original comparison participants are presented in this section.

Table XVI-3-1

HEMATOLOGICAL VARIABLES STUDIED

<u>Variable Name</u>	<u>Abbreviation</u>	<u>Units Of Measure</u>	<u>Normal Range</u>
Red Blood Cell Count	RBC	Million per Cubic mm	4.6 - 6.2
White Blood Cell Count	WBC	Thousand per Cubic mm	4.8 - 10.8
Hemoglobin	Hgb	Grams per 100 ml	14.0 - 18.0
Hematocrit	Hct	ml/100 ml	42.0 - 52.0
Mean Corpuscular Volume	MCV	Cubic Micra	80.0 - 101.0
Mean Corpuscular Hemoglobin	MCH	Micromicrogram	27.0 - 31.0
Mean Corpuscular Hemoglobin Concentration	MCHC	Percent	32.0 - 36.0
Platelet Count	PLT	Thousands Per Cubic mm	150 - 450

Table XVI-3-2 provides the results of the Ranch Hand - comparison group contrasts. The abbreviation CC is used to denote linear model analyses on continuously distributed data, DD denotes categorical log linear analyses.

Two group differences are seen in Table XVI-3-2. The Ranch Hand group has a statistically significantly larger red blood cell corpuscular volume than does the comparison group ($P = 0.05$ in the CC analysis) and, perhaps paralleling this finding on corpuscular volume, the Ranch Hand group has a larger mean corpuscular hemoglobin ($P = 0.04$ in the CC analysis).

In performing these analyses of group differences, smoking history was an important variable in essentially all instances. All of the hematological variables except RBC and MCHC increase with cigarette use. A summary of P values and slopes is provided in Table XVI-3-3.

In Table XVI-3-4 analyses are provided within the Ranch Hand group, examining for differences between exposure categories. Sample sizes in these analyses are provided in Table XVI-3-5. Table XVI-3-6 provides variable means and percents by occupation and exposure group.

Table XVI-3-2
P VALUES FOR RANCH HAND-COMPARISON GROUP DIFFERENCES,
ADJUSTED MEANS, AND ABNORMAL PERCENTAGES

Var	Anal	Group	Pack-yr	Group x Pack-yr	RH Adj'd Mean	Comp. Adj'd Mean	RH ABN %	Com ABN %
RBC	CC	0.62	0.08	0.65	5.20	5.21	NA	NA
	DD	0.36		0.71	NA	NA	7.43	6.28
WBC	CC	0.14	<0.001	0.48	7.51	7.38	NA	NA
	DD	0.62		0.83	NA	NA	12.45	11.65
HGB	CC	0.15	<0.001	0.77	16.04	15.97	NA	NA
	DD	0.97		0.65	NA	NA	3.28	3.27
HCT	CC	0.23	<0.001	0.25	46.16	46.01	NA	NA
	DD	0.62		0.32	NA	NA	8.30	7.59
MCV	CC	0.05	<0.001	0.58	89.04	88.60	NA	NA
	DD	0.70		0.71	NA	NA	3.76	3.40
MCH	CC	0.04	<0.001	0.73	30.83	30.66	NA	NA
	DD	0.005		0.64	NA	NA	46.24	39.66
MCHC	CC	0.63	0.005	0.15	34.68	34.66	NA	NA
	DD	0.47		0.84	NA	NA	9.46	10.47
PLT	CC	0.06	<0.001	0.76	276.74	271.48	NA	NA
	DD	0.16		0.33	NA	NA	1.16	1.97

Table XVI-3-3

SMOKING EFFECTS ON HEMATOLOGIC VARIABLES
AS SEEN BY CONTINUOUS VARIABLE LINEAR MODELS

<u>Variable</u>	<u>P Value for Smoking Effect</u>	<u>Dependent Variable Smoking Slope (Units/Pack-yr)</u>
RBC	0.08	-0.00089
WBC	<0.001	0.0389
HGB	<0.001	0.00743
HCT	<0.001	0.0266
MCV	<0.001	0.0675
MCH	<0.001	0.0200
MCHC	0.005	-0.00376
PLT	<0.001	0.322

Table XVI-3-4

P-VALUES FOR RANCH HAND OCCUPATION AND EXPOSURE GROUP ANALYSES

Var	Generalized Linear Model				Log Linear Model		
	Occ Cat	Exp Effect	Pack-yr Effect	Exp X Pack-yr	Exp Effect	Pack-yr Effect	Exp X Pack-yr
RBC	OFF	0.69	0.83	0.53	*	*	0.09
	ENL F.	*	*	0.03	0.83	0.66	0.59
	ENL G.	0.06	0.13	0.26	0.35	0.50	0.22
WBC	OFF	*	*	<0.001	0.52	0.47	0.62
	ENL F.	0.61	<0.001	0.26	0.51	0.06	0.75
	ENL G.	*	*	0.09	0.85	0.69	0.74
HGB	OFF	0.37	<0.001	0.68	0.27	0.32	0.56
	ENL F.	0.59	0.07	0.40	0.19	0.13	0.48
	ENL G.	0.08	0.03	0.38	0.46	0.23	0.26
HCT	OFF	0.77	<0.001	0.37	*	*	0.01
	ENL F.	0.50	0.001	0.22	*	*	0.06
	ENL G.	0.19	0.008	0.23	0.19	0.28	0.49
MCV	OFF	0.38	<0.001	0.58	0.98	0.93	0.18
	ENL F.	0.84	<0.001	0.18	0.83	0.84	0.61
	ENL G.	0.45	<0.001	0.19	0.39	0.45	0.49
MCH	OFF	0.38	<0.001	0.84	0.05	0.04	0.43
	ENL F.	*	*	0.08	0.47	0.01	0.38
	ENL G.	0.84	<0.001	0.51	0.99	0.05	0.47
MCHC	OFF	0.24	0.01	0.32	0.03	0.08	0.97
	ENL F.	0.77	0.003	0.59	0.88	0.08	0.63
	ENL G.	0.65	0.73	0.55	0.39	0.60	0.17
PLT	OFF	0.66	0.02	0.56	0.30	0.95	0.99
	ENL F.	0.26	<0.001	0.17	0.24	0.93	0.95
	ENL G.	0.97	0.91	0.71	0.32	0.88	0.58

*P values not relevant due to Exposure by Pack-year interaction term.

Table XVI-3-5

SAMPLE SIZES FOR RANCH HAND OCCUPATION
AND EXPOSURE GROUP ANALYSES

<u>Occupational Category</u> <u>Exposure Category</u>	<u>Officer</u>	<u>Enlisted</u> <u>Flying</u>	<u>Enlisted</u> <u>Ground</u>
Low	111	56	150
Medium	128	58	178
High	125	65	146

In Table XVI-3-4, 2 statistically significant ($P \leq 0.05$) overall exposure group effects are seen and 7 exposure-smoking interaction effects ($P \leq 0.10$) are also present. First, the overall exposure group effects will be described.

The 2 overall exposure group effects occur in the Ranch Hand officer cohort and involve the variables MCH and MCHC. An increasing dose-response relationship is clear in the MCH data, and the high exposure group also has the highest rate of mean corpuscular hemoglobin concentration (MCHC) abnormalities. These findings are suggestive of a herbicide effect, however, similar trends are not noted in the other 2 occupational categories thus decreasing the likelihood of a bonafide herbicide effect by raising the possibility that an unknown confounding variable is operative.

Table XVI-3-6

HEMATOLOGICAL VARIABLE MEAN AND PERCENTS FOR RANCH HAND
OCCUPATION-EXPOSURE GROUP ANALYSES

Var	Adjusted Variable Means				Percent Abnormal**		
	Exp Level	OFF	ENL Flying	ENL Ground	Officers	ENL Flying	ENL Ground
RBC	Low	5.11	5.15*	5.23	8.11	8.93	4.00
	Medium	5.07	5.20*	5.34	9.38	8.62	6.74
	High	5.11	5.24*	5.27	8.80	6.45	8.22
WBC	Low	7.03*	8.25	7.63*	11.71	16.07	12.00
	Medium	6.93*	7.91	7.66*	7.03	13.79	14.04
	High	7.15*	7.89	7.81*	10.53	21.54	12.33
HGB	Low	15.82	15.99	16.04	3.60	3.57	4.67
	Medium	15.80	16.11	16.26	2.34	1.72	2.25
	High	15.95	16.19	16.09	0.80	9.23	4.11
HCT	Low	45.36	46.22	46.36	11.71	8.93	8.00
	Medium	45.40	46.42	46.82	10.94	8.62	3.37
	High	45.59	46.84	46.39	11.20	10.77	6.16
MCV	Low	89.02	90.09	88.75	3.60	3.57	2.67
	Medium	89.84	89.53	88.10	3.91	1.72	5.06
	High	89.56	89.70	88.46	4.00	3.08	3.42
MCH	Low	30.94	31.08*	30.61	41.44	46.43	40.67
	Medium	31.14	30.97*	30.50	52.34	44.83	41.01
	High	31.22	30.91*	30.56	58.40	53.85	42.47
MCHC	Low	34.80	34.56	34.54	9.91	8.93	10.67
	Medium	34.73	34.65	34.66	6.25	6.90	6.74
	High	34.94	34.52	34.61	16.00	7.69	9.59
PLT	Low	262.13	294.48	280.94	0.00	3.57	2.67
	Medium	268.20	290.97	282.09	1.56	0.00	0.56
	High	264.09	277.78	282.53	0.00	0.00	1.37

*Unadjusted means given due to smoking (pack-years) by dependent variable interaction.

**All percents given are unadjusted.

The general linear model analysis of the red blood cell count shows an interesting interaction with smoking in Ranch Hand enlisted flying personnel. In the low exposure set of enlisted flying Ranch Handers, smoking cigarettes is associated with increasing RBC values (slope = 0.00562), but the medium exposed and high exposed individuals show decreasing RBC values with smoking (slopes -0.00124 and -0.00457 respectively). This gradient of slopes with exposure is suggestive of a true herbicide effect.

Log-linear analysis of the red blood cell count shows a smoking-exposure interaction among Ranch Hand officers. The data for these officers is given in Table XIV-3-7.

Table XVI-3-7

SMOKING-EXPOSURE INTERACTIONS ON RBC IN RANCH HAND OFFICERS

<u>Exposure</u>	<u>% ABNORMAL RBC</u>		
	<u>Zero Pk-Yrs</u>	<u>1-10 Pk-Yrs</u>	<u>>10 Pk-Yrs</u>
Low	0.00	16.67	13.16
Med	8.51	10.53	9.68
High	9.52	5.88	9.09

This interaction is compatible with an herbicide effect, and reinforces the finding in the enlisted flying personnel.

The WBC count in Ranch Hand officers shows a smoking-exposure interaction ($P < 0.001$). In the low exposure officer set, cigarette use is associated with an increased WBC value (slope = 0.0691), but this association is less in the higher exposure categories (slope in medium exposure category = 0.0251, and slope in the high exposure category is 0.0307). These data suggest that the correlation of leucocyte count to cigarette smoking might be affected by herbicide exposure in Ranch Hand officers. This pattern of decreasing association of leucocyte counts to cigarette smoking with increasing exposure is also suggested by the data for Ranch Hand enlisted ground personnel. In the low exposure set, cigarette use is also associated with increased WBC values (slope = 0.0466) but this association is least in the high exposed group (slope = 0.0192).

An exposure - pack-year interaction in the HCT data was noted in the officer cohort ($P = 0.01$) and an interaction was also seen in the enlisted flying group. The data describing these interactions is shown in Table XIV-3-8. Relatively smooth dose-response trends are seen in each officer smoking category, but the same regularity is not apparent in the enlisted flying group. It is of interest that the HCT pattern seen in the officer data of Table XIV-3-8 appears to parallel the RBC pattern in the officer data of Table XIV-3-7.

Table XIV-3-8

SMOKING-EXPOSURE INTERACTIONS ON HCT
IN RANCH HAND OFFICERS
AND ENLISTED FLYING PERSONNEL

<u>Occupation</u>	<u>Exposure</u>	<u>% Abnormal HCT</u>		
		<u>Zero Pk-yr</u>	<u>1-10 Pk-yr</u>	<u>>10 Pk-yr</u>
Officers	Low	6.12	16.67	15.79
	Med	8.51	15.79	11.29
	High	23.81	11.76	3.03
Enlisted Flying	Low	37.50	0.00	5.00
	Med	0.00	33.33	5.13
	High	18.18	16.67	7.14

Lastly, a smoking-exposure interaction is seen in the MCH data in the flying enlisted group. In the low exposure group the MCH - pack-year slope is -0.00478, while this slope is positive in the medium and high exposure sets (0.0207 and 0.03083 respectively).

Summary and Conclusions

The ranch hand group has a higher mean corpuscular volume and mean corpuscular hemoglobin than does the comparison group. Also, a dose-response pattern of increasing mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration was found in the Ranch Hand officer cohort. Seven hematologic variable by cigarette use by exposure level interactions were also found. Five of these interactions involved decreasing associations of hematologic measures with smoking with increasing exposure levels. One interaction (for MCH) showed increasing associations with smoking at increased exposure levels, and one interaction was uninterpretable.

These statistical findings display some degree of consistency. However, the statistical differences do not appear to be significant in terms of current medical morbidity.